Infectious Diseases and Tropical Medicine Research Center

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Fungal Infections in Patients with Hematological

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Challenges of Diagnosing Opportunistic Infections at the Bedside

Bacterial?

Viral?

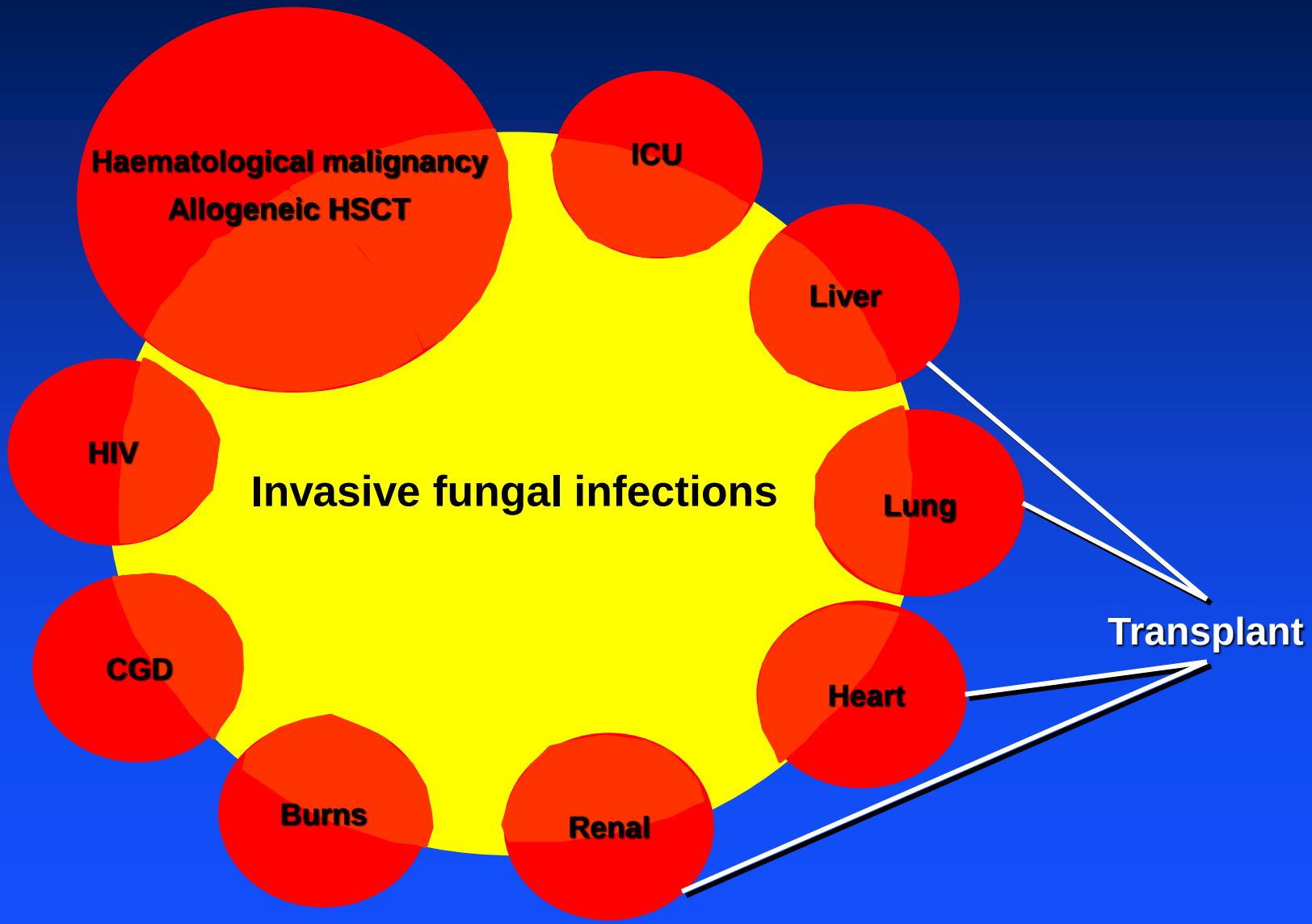
Challenges in Management of Invasive Fungal Infections (IFI) in Immunocompromised (IC) Patients

- Know the Changing Epidemiology of IFI
- Nonspecific presentation of IFI
- Inadequate diagnostic methods
- Antifungal prophylaxis – Does it work ?
- Breakthrough Infections while on antifungal therapy
- Refractory to antifungal treatment

Inadequate Current diagnostic methods for IFI >30% Detected on autopsy

- In a case series involving patients with hematologic malignancy
- IFI high prevalence of IFI 31% detected at autopsy
- 77% of the patients' deaths were related to infection
- This highlighted the inadequacies of current diagnostic methods for IFI Haematologica

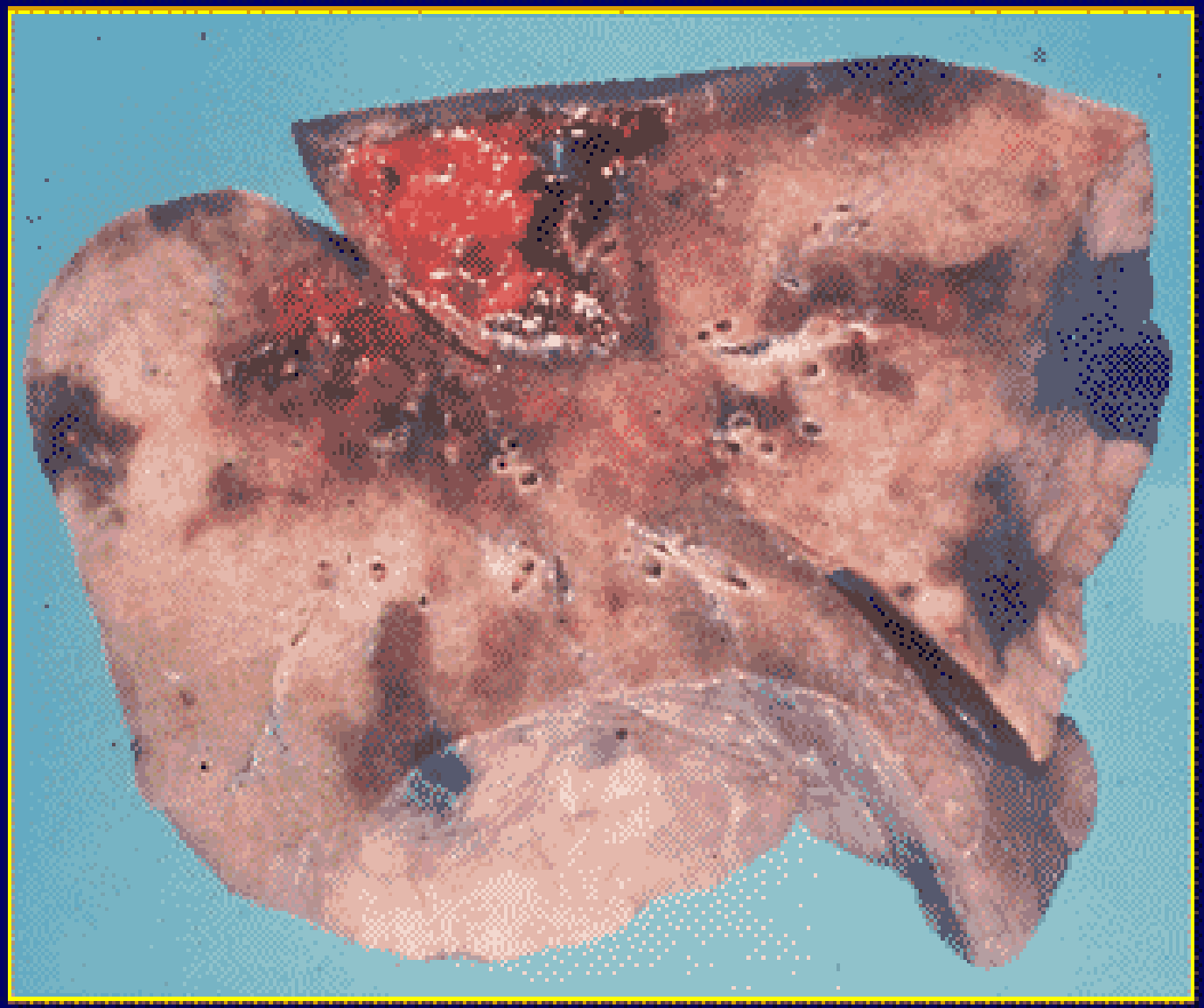
Who gets IFI?


Haematological malignancy
Allogeneic HSCT
ICU
Liver
HIV
Invasive fungal infections
Lung
Transplant
CGD
Heart
Burns
Renal

Usual fungal infections in immunocompromised patients

- Candidiasis
- Aspergillosis
- Mucormycosis
- Fusariosis
- Cryptococcosis

Invasive Aspergillosis, Lung



Young et al. *Medicine*. 1970;49:147-173.

Risk factors for development of IFIs

- Neutropenia
- Lymphopenia
- Corticosteroids
- Immunosuppressives
- Chemotherapy
- Bone Marrow Transplantation
- Broad-spectrum antibiotics
- Mucositis
- Parenteral alimentation
- Central venous catheters (CVCs)
- Hospital construction

Characteristics of 94 patients with invasive fungal disease

Characteristic	No.	Characteristic	No.
Gender male:female	50:44	Other	6 (6.4)
Age, median (range)	50.5 (16–78)	Hematopoietic cell transplantation	19 (20.2)
Underlying disease		Autologous	2/19 (10.5)
Acute Myeloid leukemia	46 (48.9)	Allogeneic	17/19 (89.5)
Acute lymphoid leukemia	12 (12.8)	Matched HLA, related donor	8/17 (47.0)
Non-Hodgkin's lymphoma	10 (10.6)	HLA-matched, unrelated donor	5/17 (29.4)
Aplastic anemia	7 (7.4)	Haploidentical	4/17 (23.6)
Chronic lymphoid leukemia	5 (5.3)	Receipt of corticosteroids within 30 days of IFD	38 (40.4)
Hodgkin's lymphoma	4 (4.3)	Receipt of other immunosuppressive agents	16 (17.0)
Multiple myeloma	4 (4.3)		

Number in parenthesis represent percentage unless specified; * other underlying disease: myelodysplasia (n = 2), chronic myeloid leukemia, dendritic cell leukemia, myelofibrosis, large granular lymphocyte leukemia (1 patienteach); HLA = human leukocyte antigen; IFD = invasive fungal disease.

Frequency and etiology of invasive fungal disease in 316 hematopoietic cell transplant recipients and in 664 patients with hematologic malignancies

Invasive Fungal Disease	Allogeneic HCT n = 191 (%)	Autologous HCT n = 125 (%)	Acute Leukemia n = 294 (%)	Other Underlying Diseases n = 370 (%)	Total n = 980 (%)
Aspergillosis	8 (4.2)	1 (0.8)	28 (9.5)	13 (3.5)	50 (5.1)
Fusariosis	6 (3.1)	0	9 (3.1)	2 (0.5)	17 (1.7)
Candidiasis	2 (1.0)	1 (0.8)	5 (1.7)	2 (0.5)	10 (1.0)
Cryptococcosis	0	0	1 (0.3)	7 (1.9)	8 (0.8)
Hyalohyphomycosis	0	0	4 (1.4)	0	4 (0.4)
Mucormycosis	0	0	2 (0.7)	0	2 (0.2)
Penicillinosis	0	0	2 (0.7)	0	2 (0.2)
Trichosporonosis	1 (0.5)		0	0	1 (0.1)
Total	17 (8.9)	2 (1.6)	51 (17.3)	24 (6.5)	94 (9.6)

The Distribution of Patients Based on Hematological Malignancy and Sex

Hematological Malignancy	Male	Female	Total
Acute myeloid leukemia	24 (45.3)	29 (54.7)	53 (44)
Hodgkin lymphoma	6 (40)	9 (60)	15 (12.5)
Chronic myelogenous leukemia	2 (16.7)	10 (83.3)	12 (10)
Multiple myeloma	2 (18.1)	9 (81.8)	11 (9.1)
Acute lymphoblastic leukemia	4 (40)	6 (60)	10 (8.3)
Myelodysplastic syndrome	2 (28.5)	5 (71.5)	7 (5.8)
Chronic lymphocytic leukemia	4 (57.1)	3 (42.9)	7 (5.8)
Non-Hodgkin lymphoma	2 (40)	3 (60)	5 (4.1)
Total	46 (38.4)	74 (61.6)	120 (100)

Epidemiology of IFI in Both SOTR and HSCT Recipients

Increasing incidence of mold infections

	SOTR	HSCT
Invasive candidiasis	53%	28%
Invasive aspergillosis	19%	43%
Cryptococcosis	8%	-
Non-aspergillus molds	8%	-
Endemic fungi	5%	-
Zygomycosis	2%	-

The Transplant-Associated Infections Surveillance Network (TRANSNET) -23 transplant centers in the US, prospective study from 2001 to 2006: epidemiology of IFI in both SOTR and HSCT recipients.

Clin Infect Dis. 2010, 50:1101–11, Clin Infect Dis. 2010, 50:1091–100

REVIEW ARTICLE

Invasive fungal infections in hematologic malignancies: Incidence, management, and antifungal therapy

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The incidence of invasive fungal infections (IFIs) has increased in recent years as a result of increasing the incidence of hematologic malignancies (HMs). IFIs, as the opportunistic diseases, are the most important concern in these patients with a high mortality rate. These infections are one of the leading causes of morbidity and mortality in HM patients and an important factor in increasing the costs of patients' management because of the prolonged hospitalization and the inevitable need to use antifungal agents. Due to the changes in the pattern of organisms causing IFIs, unavailability of effective and safe antifungal drugs, and high rate of drug resistance as well as lack of fast and accurate diagnostic methods, these infections have become a serious and life-threatening problem necessitating effective prevention and treatment strategies using suitable antifungal agents, especially in high-risk patients. The aim of the present study was to review the pathogens causing various types of IFIs, diagnostic methods, and novel prophylactic and therapeutic antifungal regimens in HM patients according to the new published studies and clinical trials.

Key words: Antifungal, fungal infection, hematologic malignancy, neutropenic fever, treatment

EPIDEMIOLOGY

1- in a study in Italy, of 538 patients with IFI, 373 patients (69%) had AML.

2-In pediatric patients, ALL is the most frequent HM related to the IFIs; this could be due to the higher prevalence of ALL than other hematological malignancies in the pediatric population.

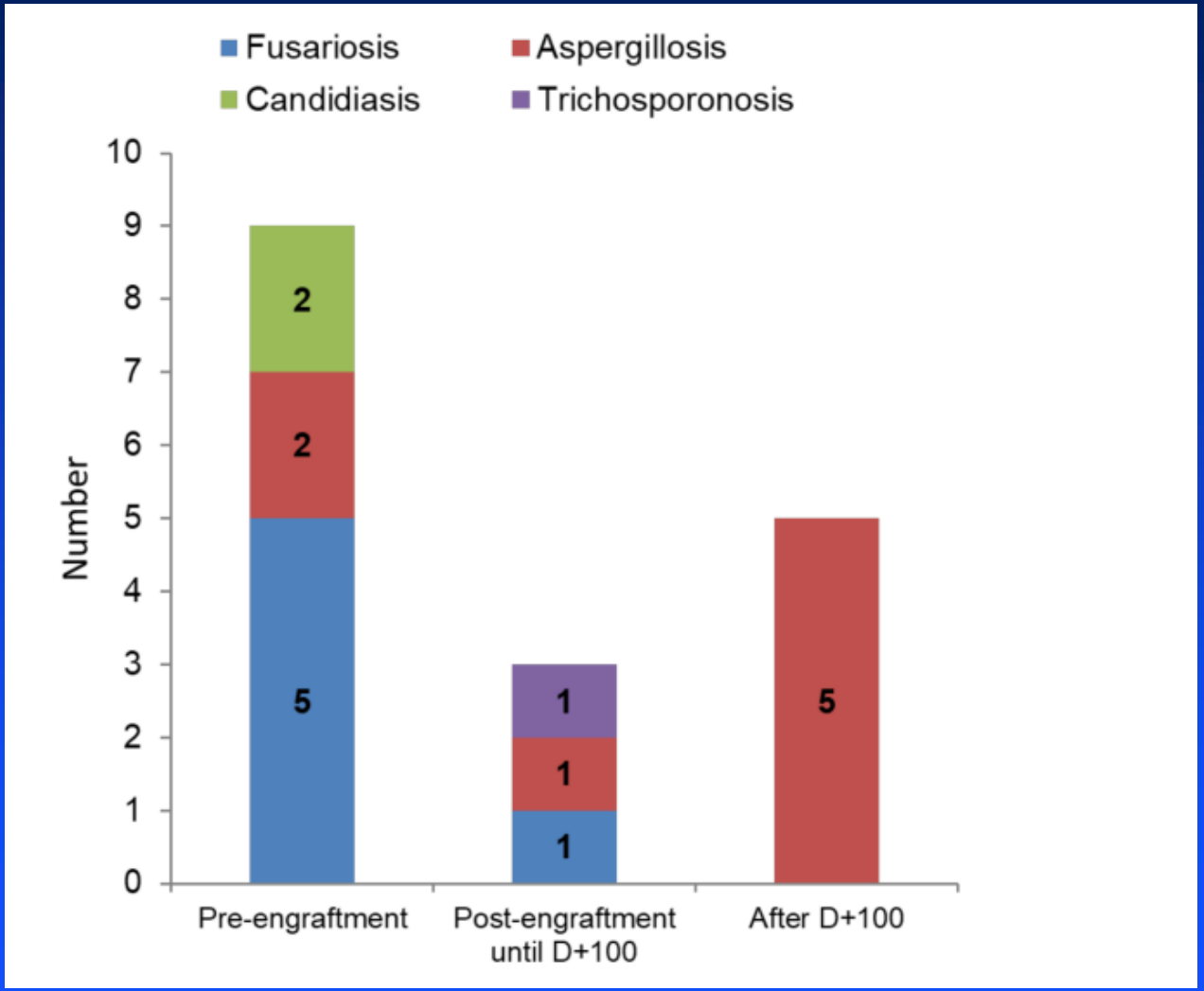
3-The prevalence range of IA is 5%–10% in AML, with mortality rate being 20%–50% that which could increase to 80% in HSCT patients.

4- In another study, the prevalence of IFIs in leukemia was about 24%, with the rate being 10%–20% in patients undergoing allogeneic HSCT.

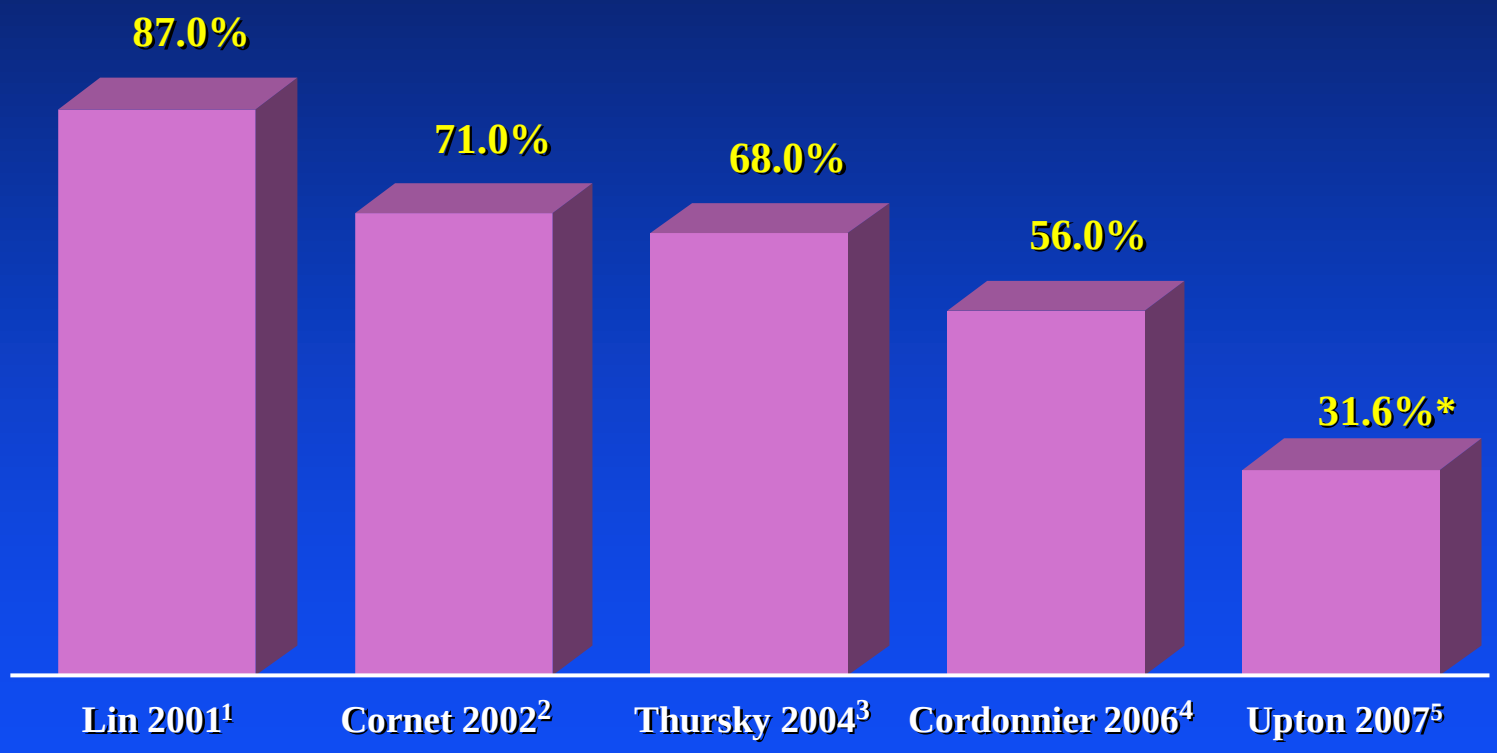
IN IRAN:

- In 2008, among a total of 4393 cases with HM in Iran, only 24 cases experienced invasive aspergillosis (IA)
- According to a recent study in Iran (2018), the prevalence of mucormycosis in Iranian HM patients was estimated as 9.2 per 100,000 of population.
- Furthermore, according to a study in 2008, the most prevalent HM developing IFI was AML, with IA being the most common infection.

Distribution of invasive fungal disease in allogeneic hematopoietic cell transplant recipients according to the period post-transplant



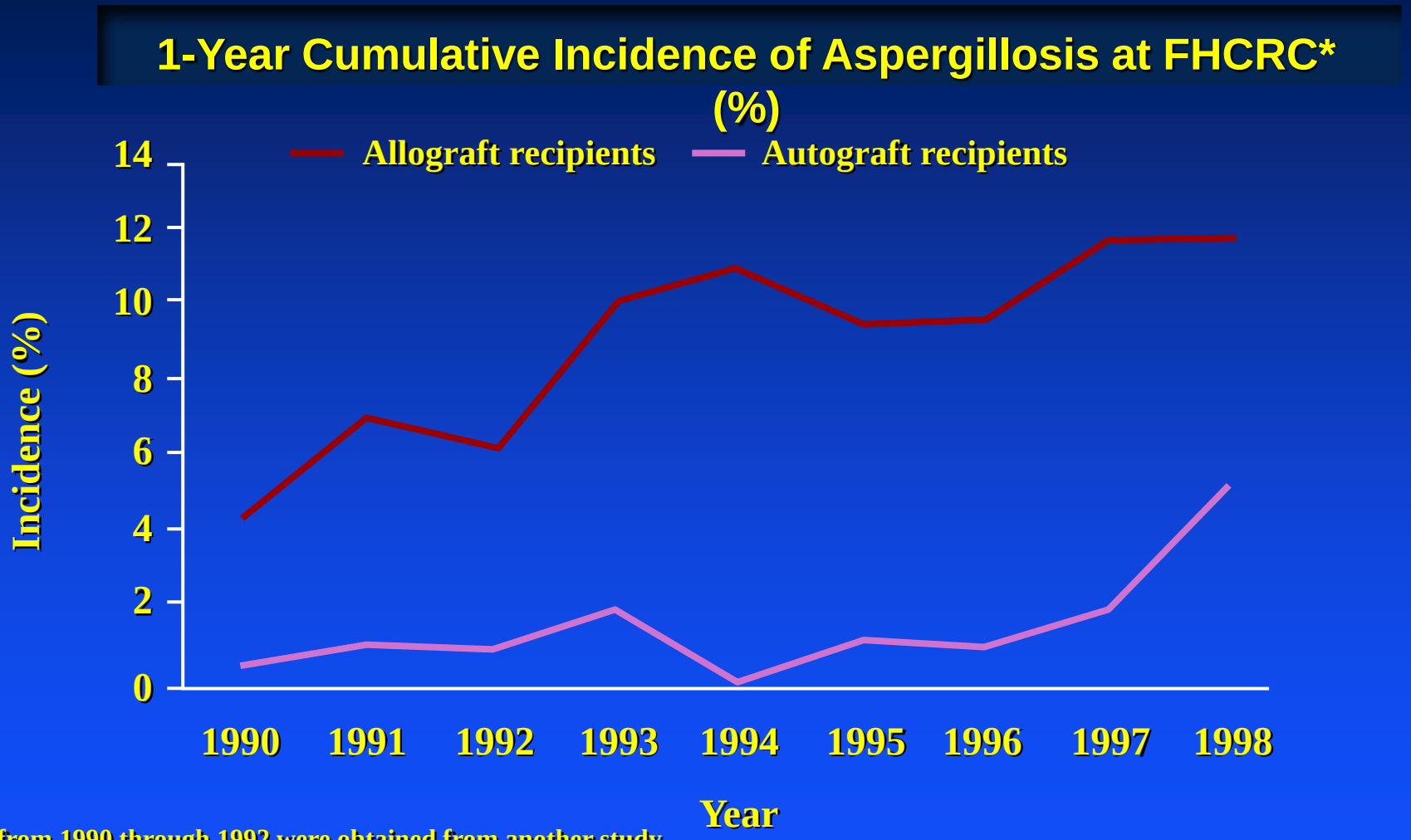
Aspergillus-Related Mortality in Allogeneic HSCT Remains Relatively High



Studies used crude mortality rate or attributable mortality rates. *Crude mortality rate at 4 months post IA diagnosis.

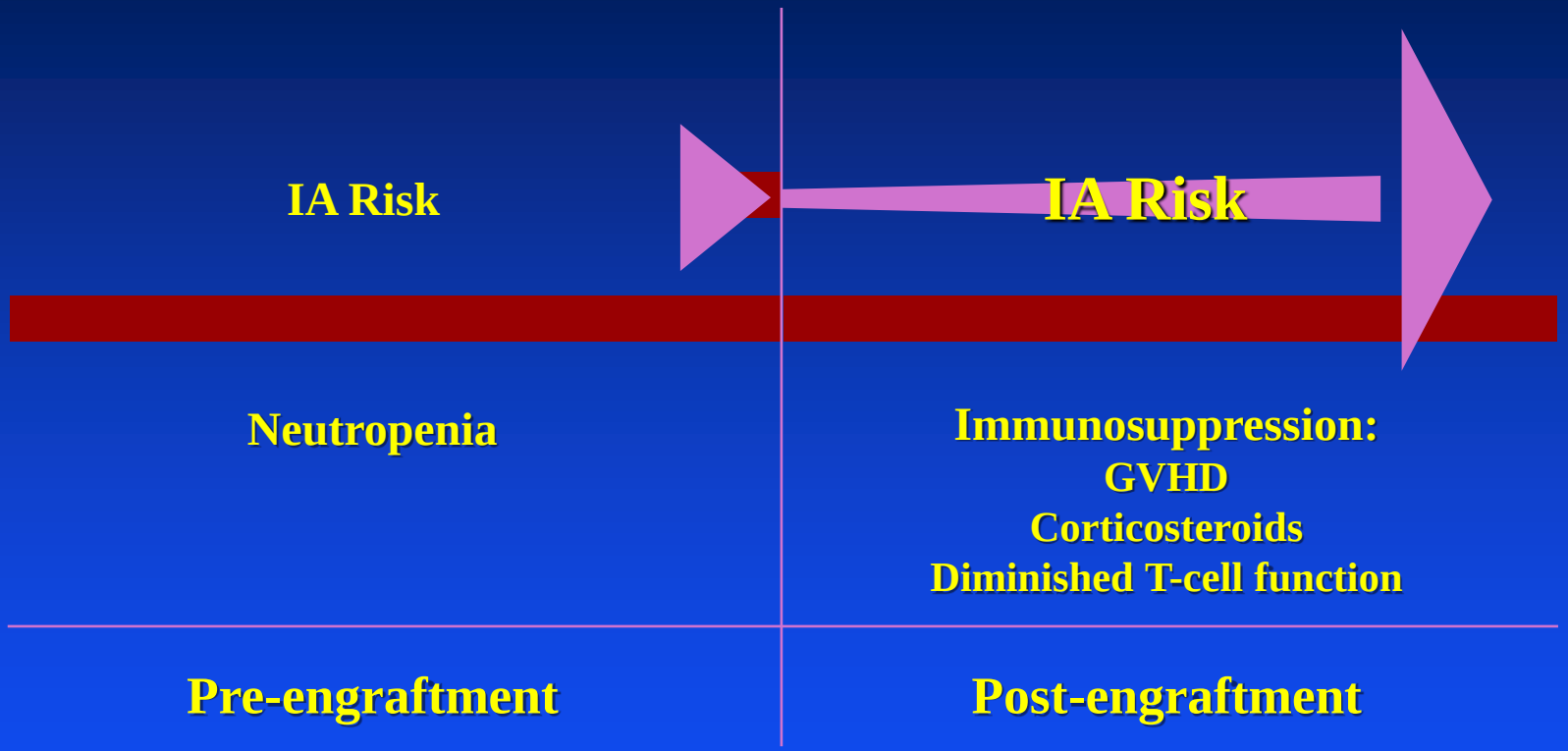
1. Lin SJ et al. *Clin Infect Dis*. 2001;32:358-366. 2. Cornet M et al. *J Hosp Infect*. 2002;51:288-296. 3. Thursky K et al. *Bone Marrow Transplant*. 2004;34:115-121. 4. Cordonnier C et al. *Clin Infect Dis*. 2006;42:955-963. 5. Upton A et al. *Clin Infect Dis*. 2007;44:531-540.

Incidence of Aspergillosis in HSCT Recipients Is Growing



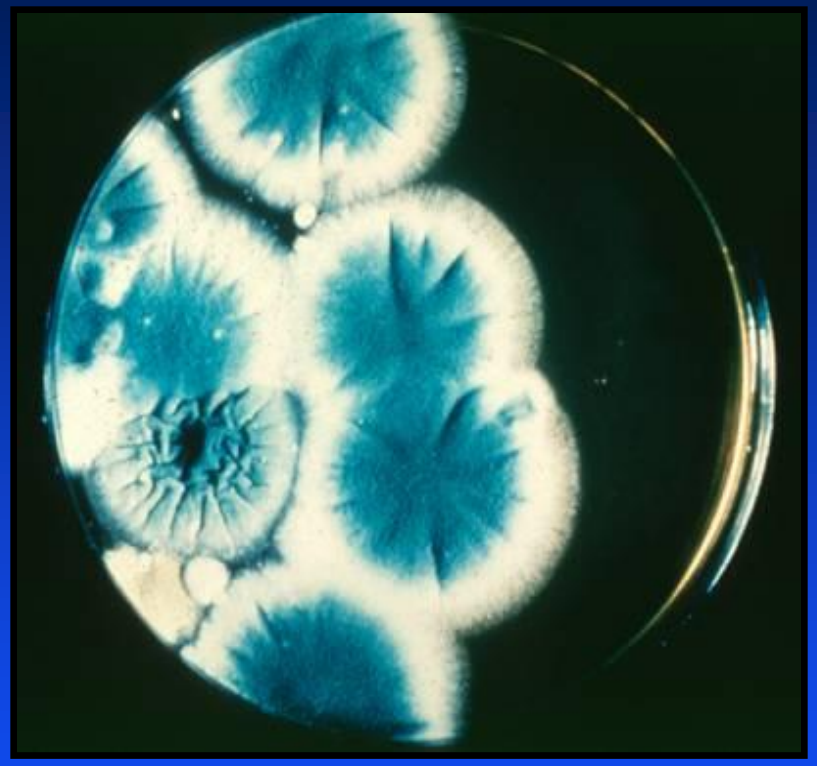
Data from 1990 through 1992 were obtained from another study.
*FHCRC, Fred Hutchinson Cancer Research Center
Adapted from Marr KA et al. *Clin Infect Dis*. 2002;34:909-917.

Invasive Aspergillosis Risk Increases During the Post-Engraftment Period



1. Marr KA. *Oncology*. 2001;15:15-19. 2. Hagen EA et al. *Clin Infect Dis*. 2003;36:9-15.

Invasive Aspergillosis
Role of Early Diagnosis & Therapy



Have We Made Progress??

Some issues

Microscopy and culture are essentially unavailable to microbiologists with respect to invasive fungal infections (IFI)

Because

- **IFI commonly affects the lungs initially but cases can easily go unnoticed**
- **Even when recognized early, suitable specimens can be difficult to obtain**
- **Tests for detecting fungal pathogens in clinical material (particularly blood) are available, but there is no consensus about their clinical utility**

Probable Invasive Pulmonary Mold Diseases

Host factors
Recent history of neutropenia (<0.5 ×10 neutrophils/L [<500 neutrophils/ mm] for >10 days) temporally related to the onset of invasive fungal disease
Hematologic malignancya
Receipt of an allogeneic stem cell transplant
Receipt of a solid organ transplant
Prolonged use of corticosteroids (excluding among patients with allergic bronchopulmonary aspergillosis) at a therapeutic dose of ≥0.3 mg/kg corticosteroids for ≥3 weeks in the past 60 days
Treatment with other recognized T-cell immunosuppressants, such as calcineurin inhibitors, tumor necrosis factor-a blockers, lymphocytespecific monoclonal antibodies, immunosuppressive nucleoside analogues during the past 90 days
Treatment with recognized B-cell immunosuppressants, such as Bruton’s tyrosine kinase inhibitors, eg, ibrutinib
Inherited severe immunodeficiency (such as chronic granulomatous disease, STAT 3 deficiency, or severe combined immunodeficiency)
Acute graft-versus-host disease grade III or IV involving the gut, lungs, or liver that is refractory to first-line treatment with steroids

Clinical features
Pulmonary aspergillosis
The presence of 1 of the following 4 patterns on CT:
Dense, well-circumscribed lesions(s) with or without a halo sign
Air crescent sign
Cavity
Wedge-shaped and segmental or lobar consolidation
Other pulmonary mold diseases
As for pulmonary aspergillosis but also including a reverse halo sign
Tracheobronchitis
Tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar seen on bronchoscopic analysis
Sino-nasal diseases
Acute localized pain (including pain radiating to the eye)
Nasal ulcer with black eschar
Extension from the paranasal sinus across bony barriers, including into the orbit
Central nervous system infection
1 of the following 2 signs:
Focal lesions on imaging
Meningeal enhancement on magnetic resonance imaging or CT

Mycological evidence
Any mold, for example, Aspergillus, Fusarium, Scedosporium species or Mucorales recovered by culture from sputum, BAL, bronchial brush, or aspirate
Microscopical detection of fungal elements in sputum, BAL, bronchial brush, or aspirate indicating a mold
Tracheobronchitis
Aspergillus recovered by culture of BAL or bronchial brush
Microscopic detection of fungal elements in BAL or bronchial brush indicating a mold
Sino-nasal diseases
Mold recovered by culture of sinus aspirate samples
Microscopic detection of fungal elements in sinus aspirate samples indicating a mold
Aspergillosis only
Galactomannan antigen
Antigen detected in plasma, serum, BAL, or CSF
Any 1 of the following:
Single serum or plasma: ≥1.0
BAL fluid: ≥1.0
Single serum or plasma: ≥0.7 and BAL fluid ≥0.8
CSF: ≥1.0
Aspergillus PCR
Any 1 of the following:
Plasma, serum, or whole blood 2 or more consecutive PCR tests positive
BAL fluid 2 or more duplicate PCR tests positive
At least 1 PCR test positive in plasma, serum, or whole blood and 1 PCR test positive in BAL fluid
Aspergillus species recovered by culture from sputum, BAL, bronchial brush, or aspirate

Probable invasive fungal diseases (IFD) requires the presence of at least 1 host factor, a clinical feature and mycologic evidence and is proposed for immunocompromised patients only, whereas proven IFD can apply to any patient, regardless of whether the patient is immunocompromised. Probable IFD requires the presence of a host factor, a clinical feature, and mycologic evidence. Cases that meet the criteria for a host factor and a clinical feature but for which mycological evidence has not been found are considered possible IFD. (1,3)-beta-D glucan was not considered to provide mycological evidence of any invasive mold disease.

Diagnostic dilemma

1-Non-specific and often overlapping signs and symptoms render fungal infections clinically undifferentiated from bacterial infections

2-Cough, pleural pain, or hemoptysis are also common symptoms observed in bacterial and viral lung infections

3-Dysphagia and retrosternal burning caused by fungal oesophagitis, is a common symptom of viral ulcers (herpes virus), and high-dose cytosine arabinoside

4-Recurring febrile episodes following initial defervescence or unexplained fever despite the administration of broad-spectrum antibiotics should raise the suspicion of IFI.

Diagnosis

1-The negative predictive value of PCR is high. The positive predictive value of PCR is considerably higher in BAL specimens in comparison to blood specimens

2-In high-risk individuals, PCR as a screening test for IFI had only a moderate degree of diagnostic accuracy

3-Despite the fact that antifungal medication before BAL sampling significantly decreases the performance of the PCR assay in HM patients

4-a positive PCR test may be able to detect breakthrough infections or a lack of response to antifungal treatment and thus may help in decision-making for intensification or modification of antifungal treatment

Diagnosis

1-Yeast in a nonsterile sample such as sputum and BAL are generally considered contamination or colonizers, even in high-risk patients.

2- By comparison, molds in the same samples are considered as possible evidence of fungal pneumonia.

3-Yeast in urine samples from a non-catheterized and severely neutropenic patient may be an indication of IFI.

Diagnosis

1-In the absence of microscopic or cultural evidence, a multidisciplinary diagnostic approach including assessment of clinical signs and symptoms

2- non-cultural mycological techniques such as biomarkers [galactomannan (GM), β-D Glucan (BDG)], molecular assays

3- imaging procedures, and endoscopic methods may be applied for the diagnosis and monitoring of IFI

Diagnosis

1-A number of studies have shown that the GM ELISA assay in BAL specimens from granulocytopenic patients has 80%–100% sensitivity and 90%–100% specificity

2-GM may give a false positive result in patients with multiple myeloma and a false negative result in patients on antifungal therapy despite the presence of an active IFI.

3-Glycoprotein antigen present in the cell wall of A. fumigatus can be detected by Aspergillus lateral flow device (Aspergillus-LFD) in serum or BAL with a sensitivity of 83% and specificity of 87%

4-The overall, sensitivities and specificities of another biomarker, (1 → 3)β-D-glucan (BDG), present in the cell wall of Candida and most pathogenic fungi range from 55% to 95% and 77%–96% respectively in HM patients

5-BGD does not allow differentiation between yeast and mold infections and may produce frequent false-negative results in cryptococcal infections (low or absent) and mucormycosis (do not produce BGD).

Imaging

1-Recent data relating to the role of imaging in the diagnosis of IPA and pulmonary mucormycosis (PM) in adults suggest that a high-resolution CT scan (HRCT) is preferred to chest radiographs, magnetic resonance imaging (MRI), and positron emission tomography (PET).

2-Among patients with IPA, nodules or infiltrates with a halo sign remain useful among neutropenic patients but they are nonspecific for IPA in other groups

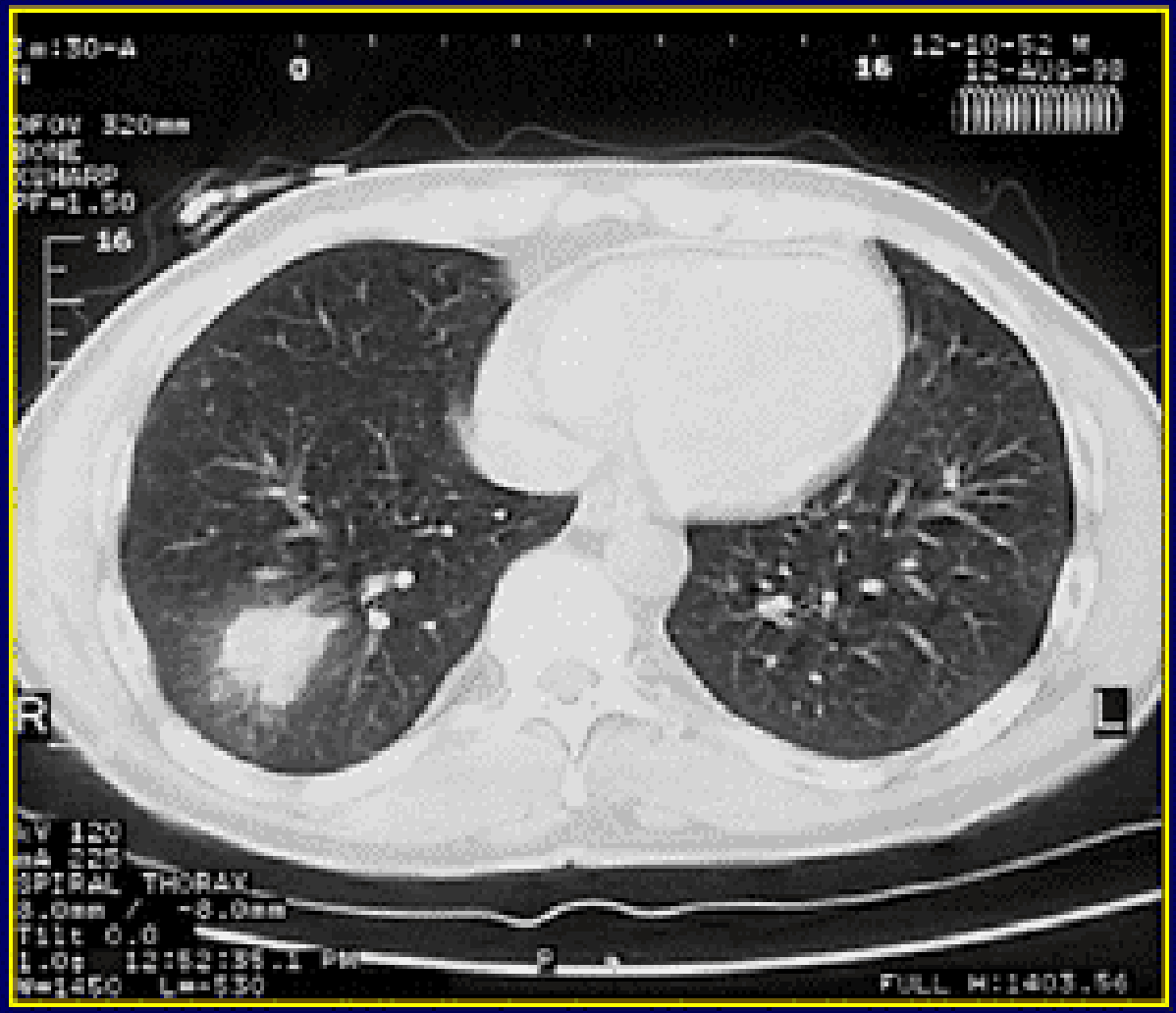
3-The air crescent sign is a late and nonspecific sign. Among nonneutropenic patients.

4-Consolidation is the most frequent presentation of PM, followed by mass lesions, nodules, and cavitation

5-Multiple nodules (more than10) and pleural effusions appear to be more frequent in PM than in IPA

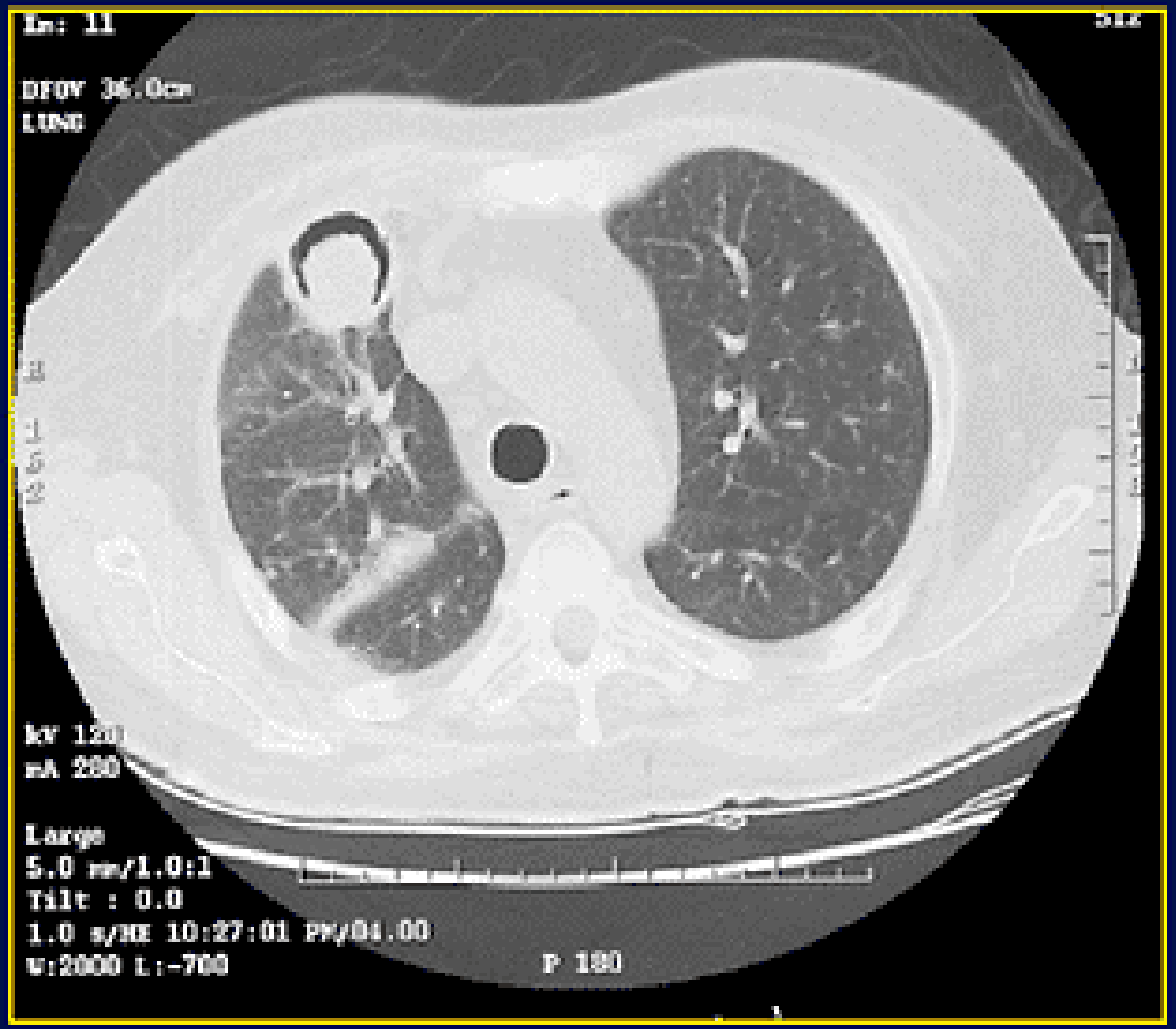
6-The reverse halo sign is more specific for PM than IPA, although the differential diagnosis also includes other diseases including tuberculosis

"Halo" Sign on CT of Neutropenic Patient With Aspergillosis



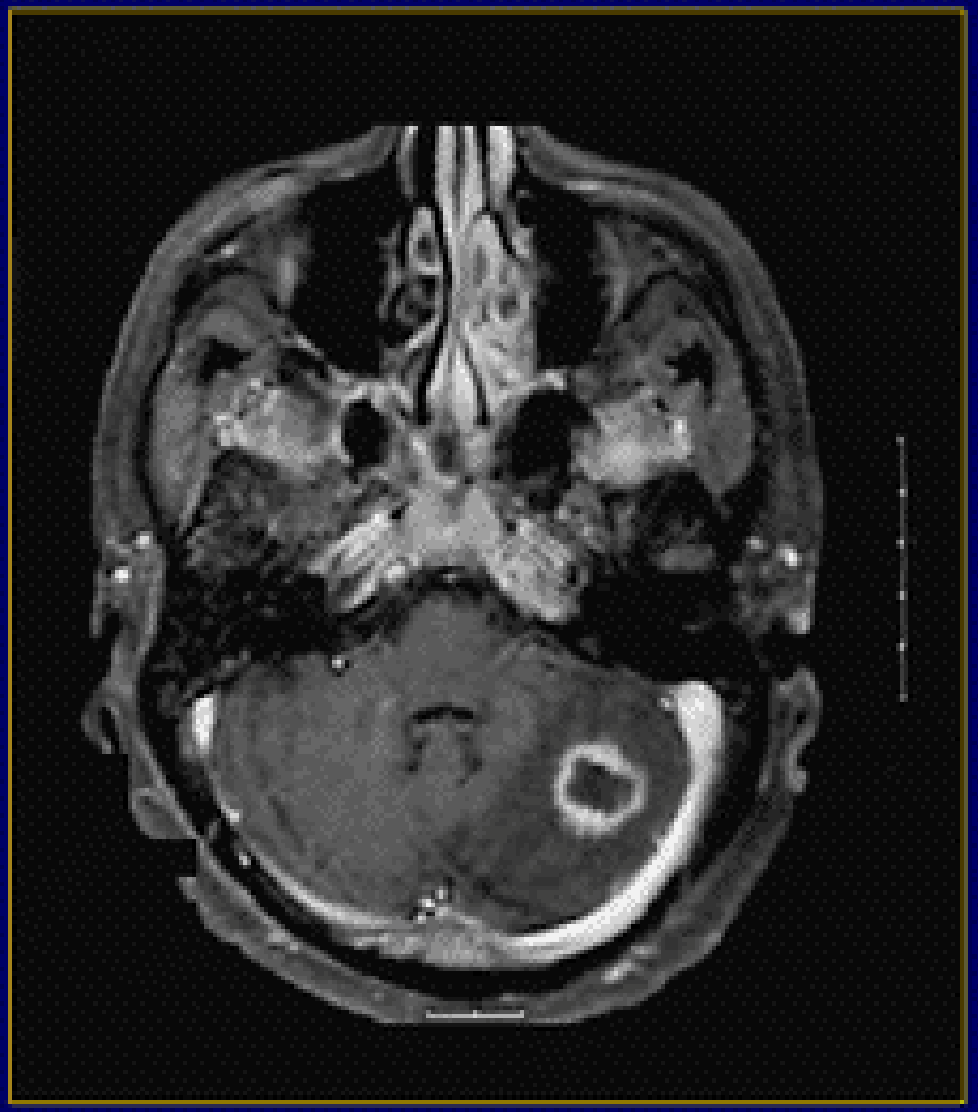
Data on file. Pfizer Inc.

Invasive Aspergillosis, Lung CT



Data on file. Pfizer Inc.

Cerebral Aspergillosis



Data on file. Pfizer Inc.

Non-Culture Based Diagnosis of Invasive Aspergillosis

Galactomannan

- **Sandwich ELISA (Platelia)**

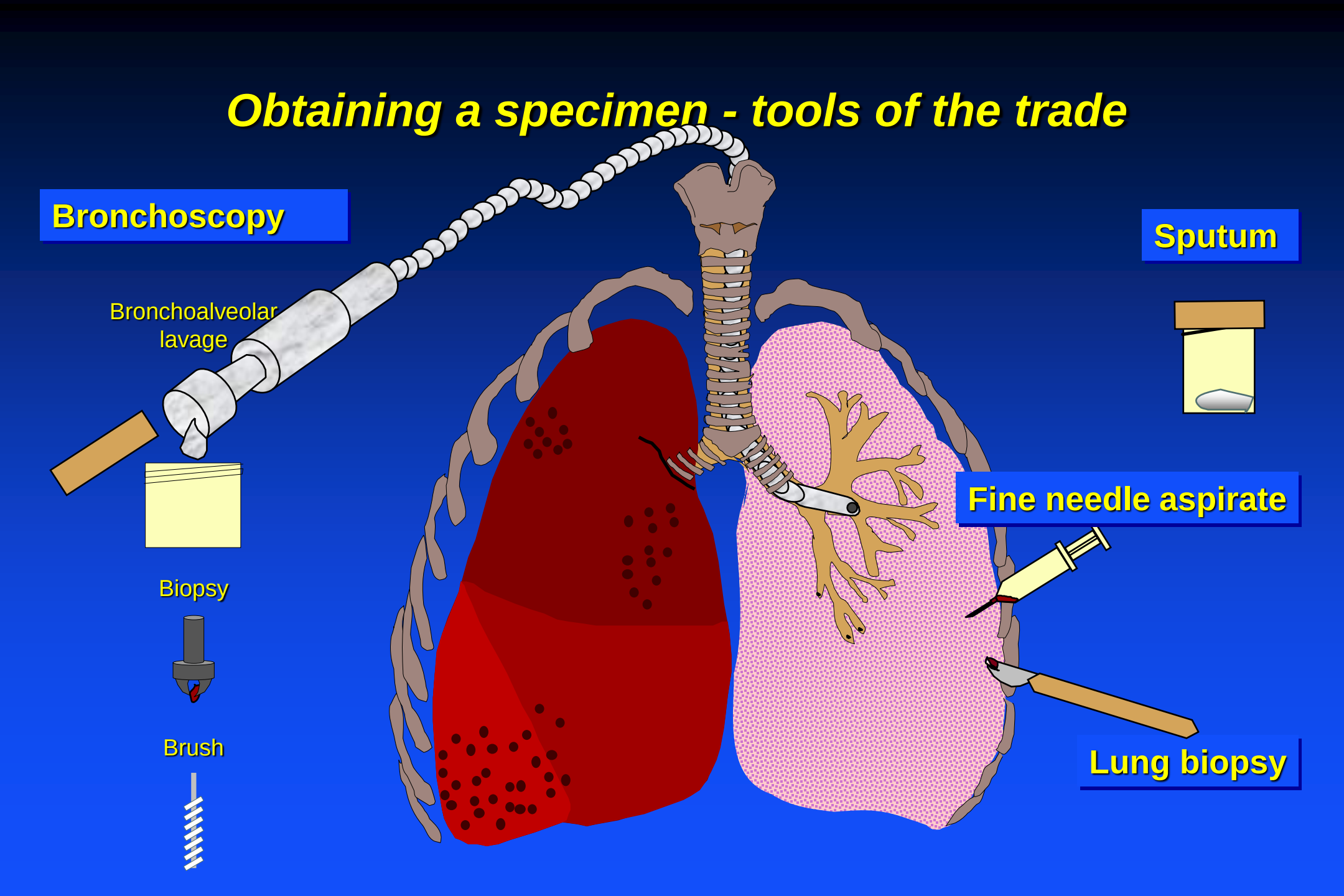
PCR

- **18s ribosomal DNA**
- **Multi-copy or single target genes**

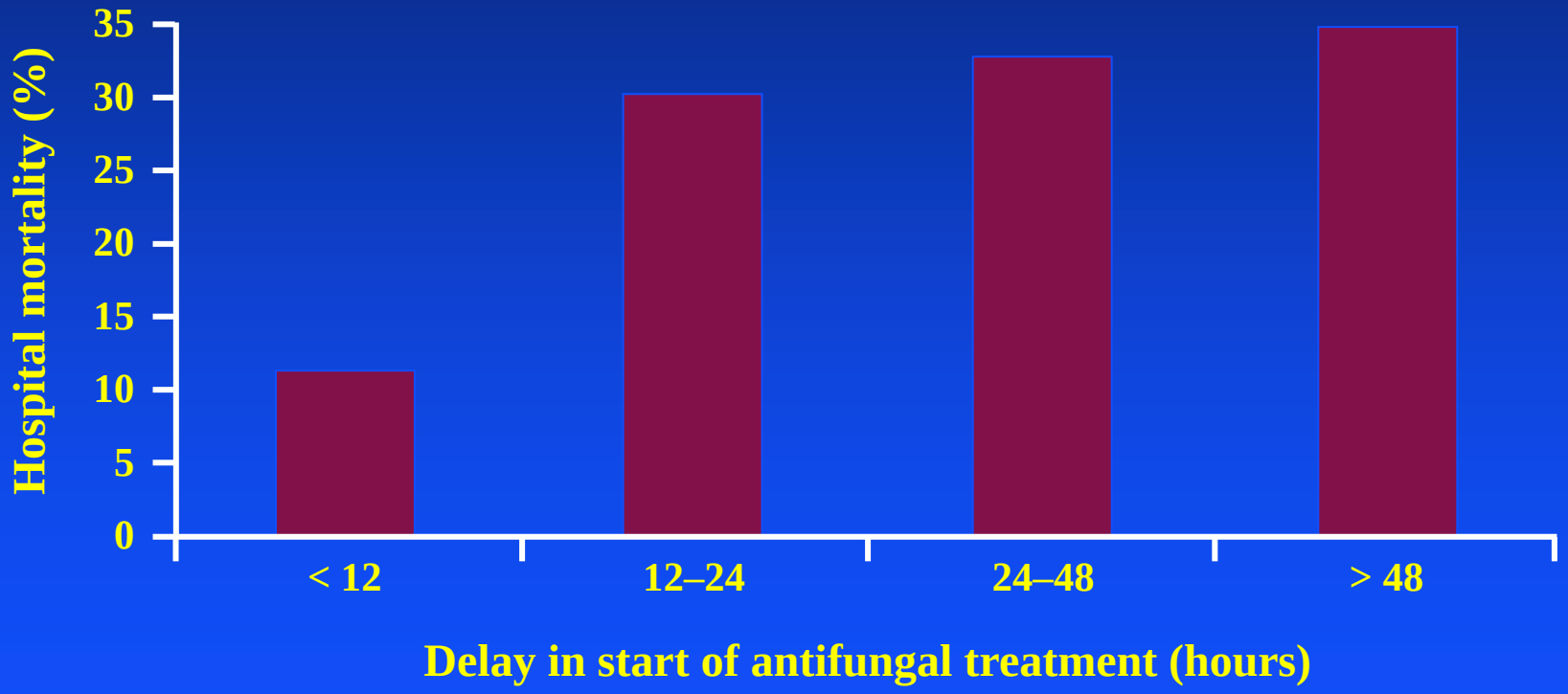
β-D-glucan

- **Amebocyte *Limulus* lysate**
- **Chromogenic (Glucatell, FungiTec G)**
- **Kinetic (Wako)**

Obtaining a specimen - tools of the trade

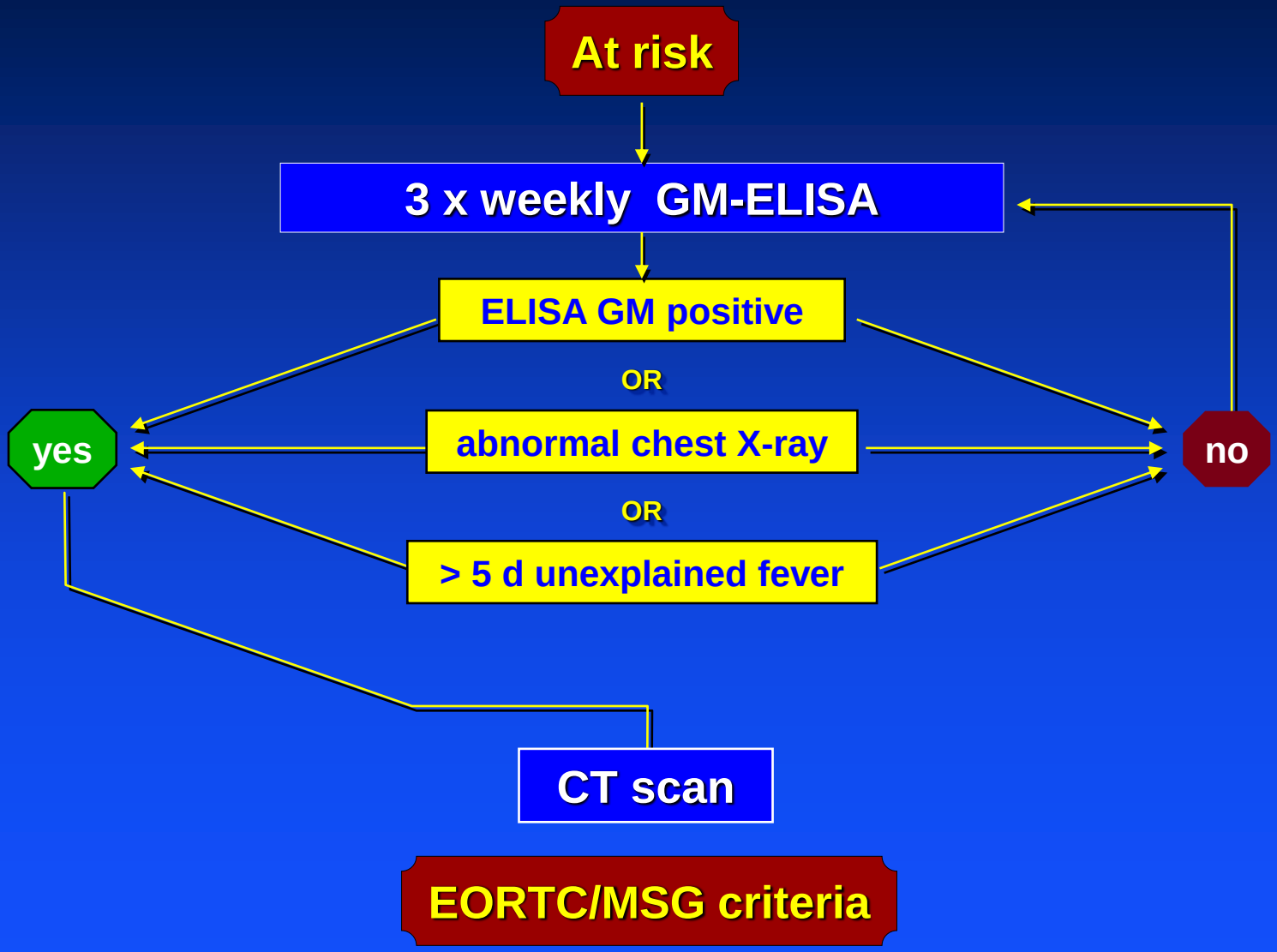


Relationship between hospital mortality and the timing of antifungal treatment

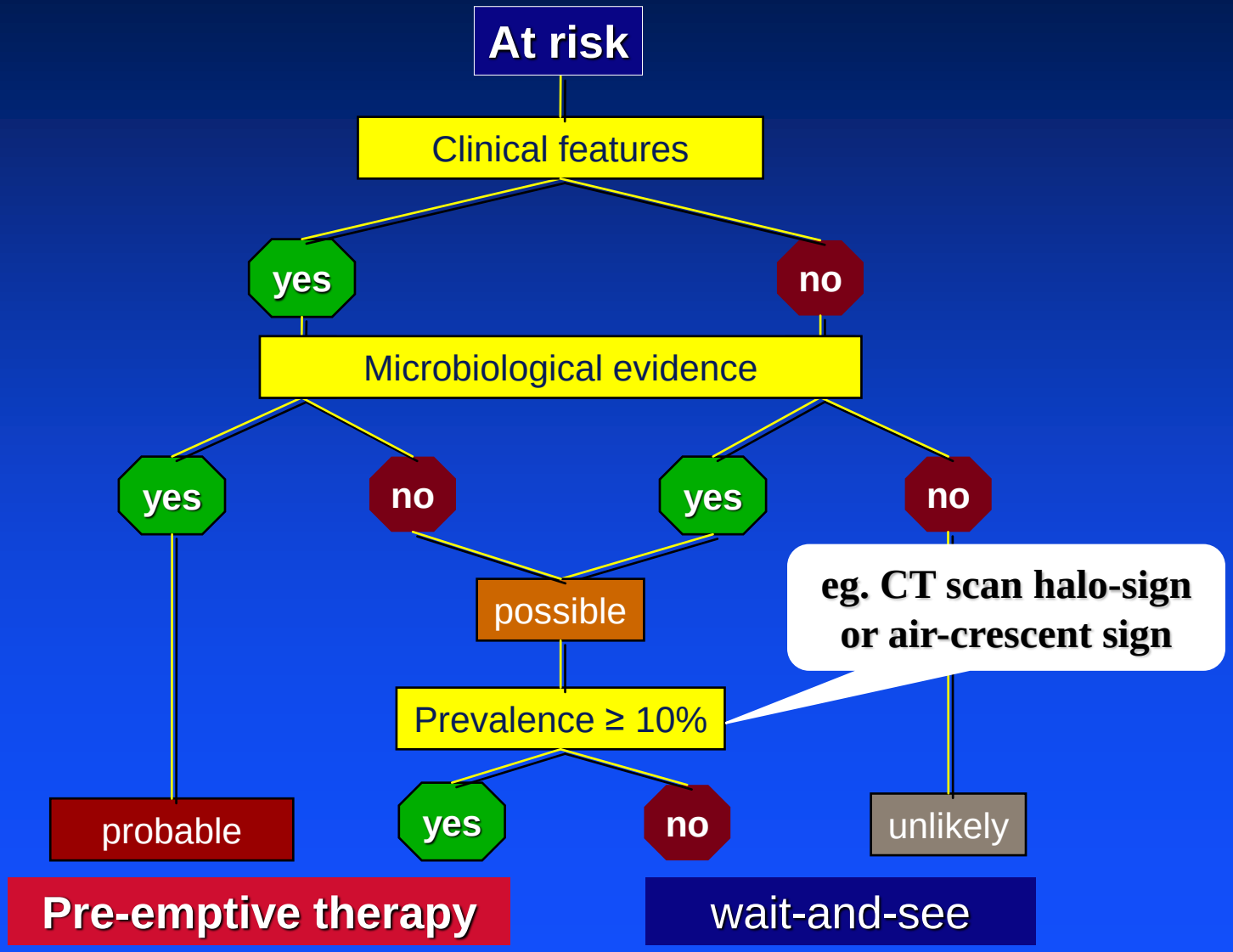


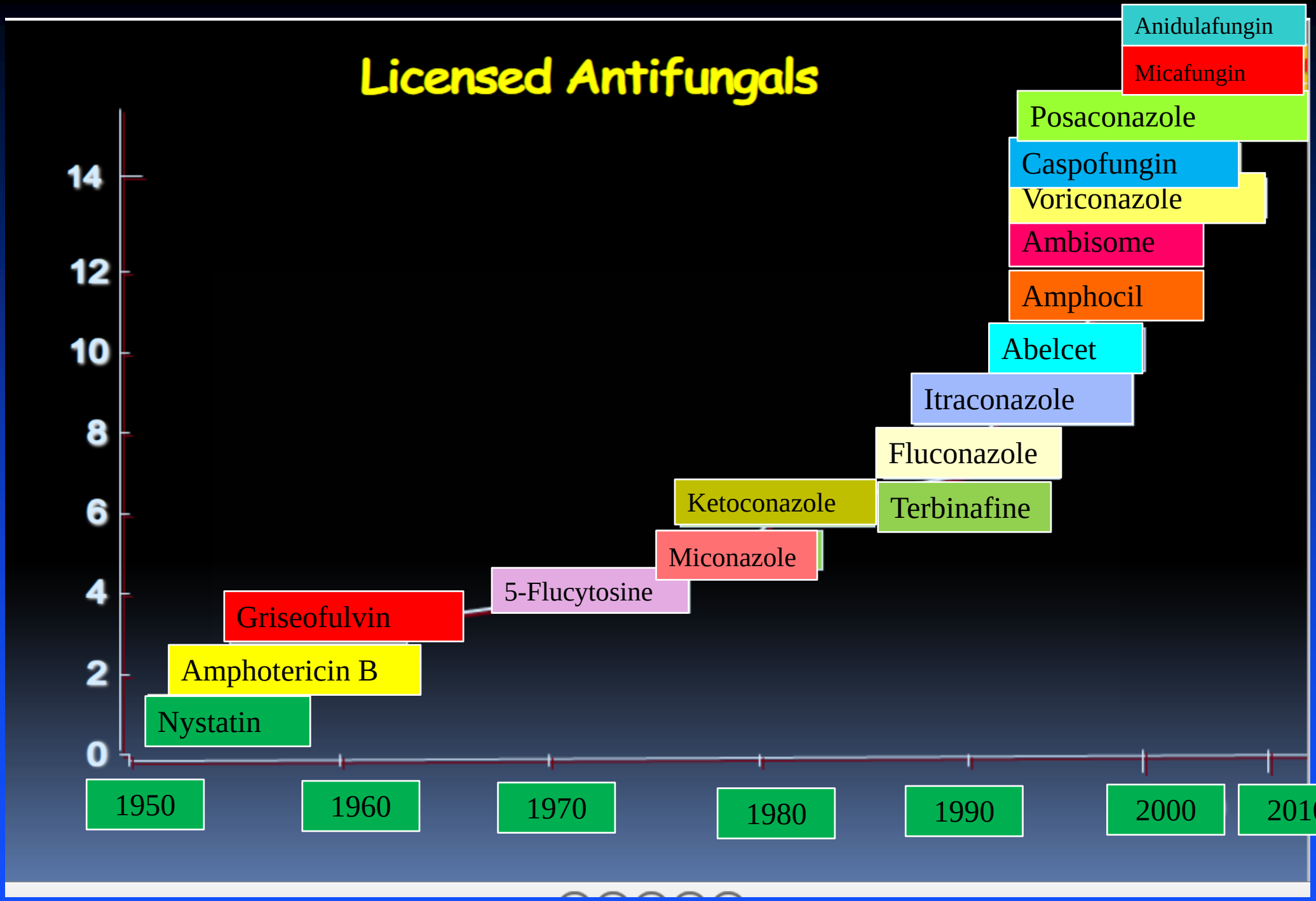
Morrell M, *et al*. *Antimicrob Agents Chemother* 2005; 49:3640–5

A strategy for managing pulmonary aspergillosis



A strategy


At risk
Clinical features
yes
no
Microbiological evidence
yes
no
yes
no
possible
eg. CT scan halo-sign
or air-crescent sign
Prevalence ≥ 10%
probable
yes
no
unlikely
Pre-emptive therapy
wait-and-see


Licensed Antifungals
14
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1950
1960
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Nystatin
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Griseofulvin
5-Flucytosine
Miconazole
Ketoconazole
Terbinafine
Fluconazole
Itraconazole
Abelcet
Amphocil
Ambisome
Voriconazole
Caspofungin
Posaconazole
Micafungin
Anidulafungin

Antifungal Susceptibility Testing Against Yeast Species Isolated From Patients with Hematological Malignancies

Candida species	Antifungal	Breakpoints, μg/mL	Number of Isolates	Resistance, %
C. albicans (n = 110)	Fluconazole	R > 8	3	2.7
		I = 4	28	
		S ≤ 2	79	
	Amphotericin B	R > 1	2	1.8
		S ≤ 1	108	
	Caspofungin	R ≥ 1	0	0
		I = 0.5	2	
		S ≤ 0.25	108	
C. glabrata (n = 8)	Fluconazole	R > 64	0	0
		I ≤ 32	4	
		S = ND	4	
	Amphotericin B	R > 1	1	12.5
		S ≤ 1	7	
	Caspofungin	R ≥ 0.5	0	0
		I = 0.25	1	
		S ≤ 0.12	7	
C. africana (n = 2	Fluconazole	R > 8	1	50
		I = 4	1	
		S ≤ 2	-	
	Amphotericin B	R > 1	1	50
		S ≤ 1	1	
	Caspofungin	R ≥ 1	-	0
		I = 0.5	-	
		S ≤ 0.25	2	

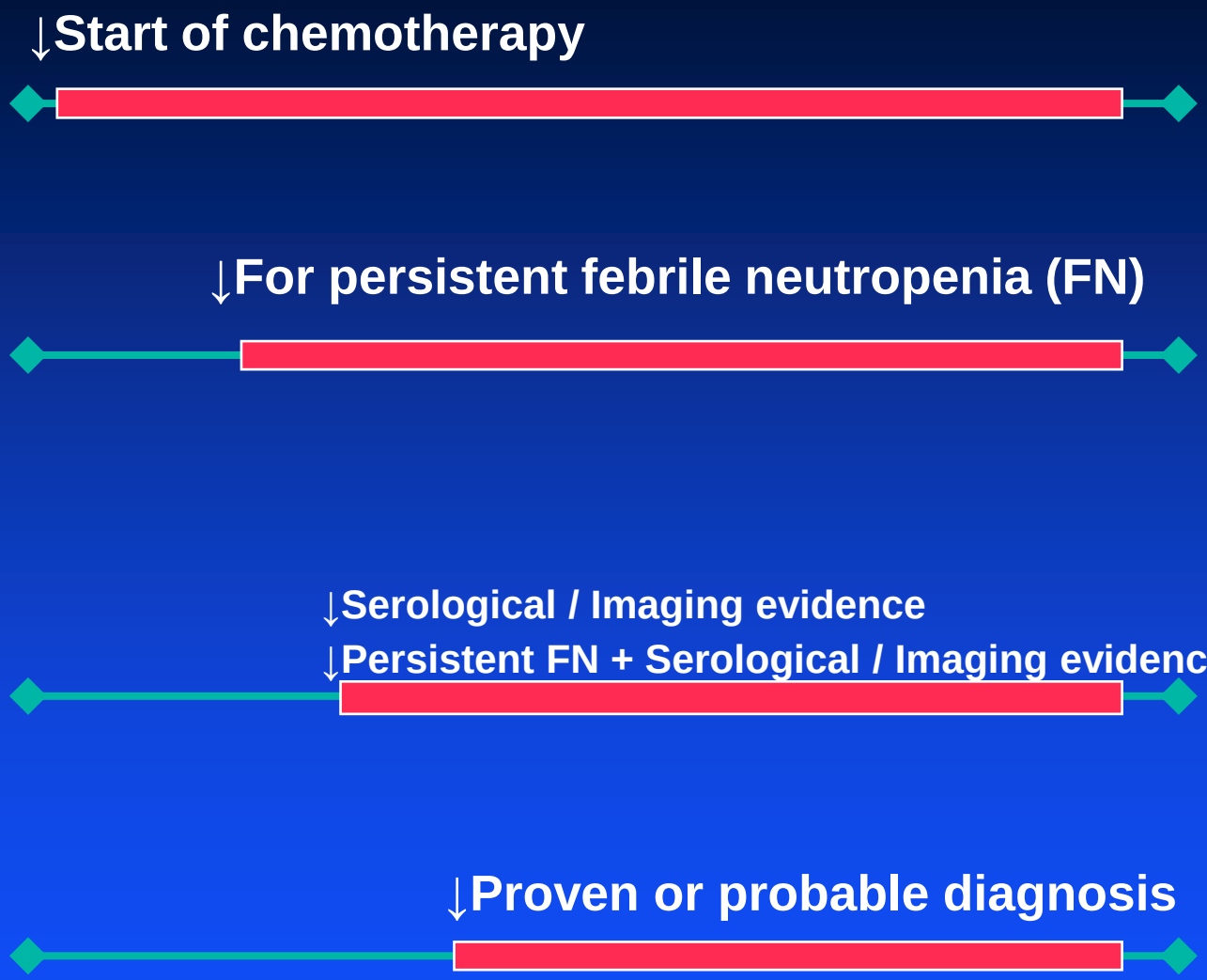
Which approach should we choose to prevent invasive fungal infection?

1. Prophylaxis
2. Empiric therapy
3. Preemptive/presumptive therapy

… depends on the intensity of immunosuppression

and environment where the patient is treated.

Timing to start antifungal agents



Recommendations for Antifungal Prophylaxis

Type of Prophylaxis	Population	Recommendation	Timing of Prophylaxis
Antifungal	Patients at high risk of febrile neutropenia or profound, protracted neutropenia Patients with GVHD	Oral triazole or parenteral echinocandin prophylaxis is recommended; a mold-active triazole is recommended when the risk of invasive aspergillosis is > 6%, such as in patients with AML/MDS or during treatment of GVHD1	During period of expected neutropenia

Patients who are expected to have profound, protracted neutropenia, which is defined as < 100 neutrophils/mL for > 7 days or other risk factors

Antifungal Prophylaxis of Patients with Hematological Malignancies Receiving Chemotherapy

Hematological Malignancies	Prophylaxis		Without Prophylaxis	Cases
	Voriconazole	Fluconazole		
Acute myeloid leukemia	36 (75)	10 (21)	2 (4)	48
Hodgkin lymphoma	3 (30)	7 (70)	0	10
Chronic myelogenous leukemia	2 (25)	6 (75)	0	8
Multiple myeloma	5 (38)	8 (62)	0	13
Acute lymphoblastic leukemia	4 (36)	7 (64)	0	11
Myelodysplastic syndrome	10 (83)	2 (17)	0	12
Chronic lymphocytic leukemia	0	8 (100)	0	8
Non-Hodgkin lymphoma	3 (30)	7 (70)	0	10
Total cases				120

TREATMENT

1-An empiric antifungal agent is indicated in high-risk patients with prolonged (>4 days) fever, in whom no specific cause has been detected by reassessment.

2-In patients who have not been on antifungal prophylaxis (usually fluconazole), Candida spp. are the most common cause of IFIs. In these patients, caspofungin (or another echinocandin) is an appropriate choice.

3-In a randomized trial that compared caspofungin with liposomal amphotericin B in 1095 patients with persistent neutropenic fever, the overall efficacy and the rates of fungal infections and fever resolution were equal in both groups

4-In patients receiving prophylaxis, fluconazole-resistant Candida spp. and invasive mold infections, especially aspergillosis, are the most likely causes.

TREATMENT

5-Patients with pulmonary nodules or nodular pulmonary infiltrates are more likely to have invasive mold infection.

6-In these situations, voriconazole or a lipid formulation of amphotericin B are preferred

7-The choice of the initial agent is dependent to the most likely diagnosis. In situations which mucormycosis is also a suspected differential diagnosis, amphotericin B is preferred, while when aspergillosis is the most likely IFI, voriconazole is usually selected as the first choice

8-In spite of in vitro activity against Aspergillus spp., echinocandins are unable to completely kill or inhibit these species.

Prophylaxis

1-Posaconazole is recommended for primary prophylaxis in AML and MDS patients undergoing intensive induction therapy.

2-Fluconazole can be used as an alternative.

3-Polyenes are always discouraged except in high-risk patients where liposomal amphotericin B in aerosolized formulations along with fluconazole may have a therapeutic advantage.

4-Fluconazole remains probably the best choice to prevent mucosal yeast infections in other HMs as there are no clear recommendations for antifungal prophylaxis.

Prophylaxis

5-Fluconazole is advised for low-risk individuals as a main prophylactic during the allogeneic HSCT pre-engraftment phase.

6-itraconazole, posaconazole, and voriconazole are recommended for high risk patients.

7-Posaconazole is also strongly recommended in the postengraftment phase when accompanied by other risk factors such as severity and unresponsiveness to corticosteroid therapy

Treatment

Definitions of anti-fungal treatment strategies.

Strategy	Definition
Prophylaxis	Patients at high riska of IFI without typical signs and symptoms
Empiric	Patients at high riska of IFI with established clinical signs and symptoms of infection, but without a known source
Pre-emptive	Patients at high riska of IFI with radiographic signs and/or laboratory tests yielding a result conclusiveof IFI, without definitive histopathological and/or cultural pathogen identification
Targeted	Diagnostic criteria permit pathogen identification

Treatment of invasive fungal infection according tothe Infectious Diseases Working Party (AGIHO)

Pathogen	Treatment	Remarks
Invasive aspergillosis	1st line: Voriconazole/Isavuconazole 2nd line: Posaconazole	Alternative therapy: Itraconazole (Voriconazole/Isavuconazole or Posaconazole is not available) Liposomal-Amphootericin B
Invasive candidasis	1st line: Echinocandins 2nd line: Fluconazole or Voriconazole	Early catheter removal is recommended whenever possible
Mucormycosis	1st line: lipid-based Amphotericin B 2nd line: Isavuconazole or Posaconazole	Surgical resection of the focus Voriconazole is inactive in mucormycosis
Cryptococcosis	1st line: Lipid-based Amphotericin B + flucytosine (5-FC) followed by maintenance therapy with Fluconazole 2nd line: Liposomal Amphotericin B+Fluconazole	Echinocandinsare not active against Cryptococcus spp. Breakthrough disseminated cryptococcal disease has been reported
Fusariosis	Lipid-based Amphotericin B or Voriconazole	Posaconazole might be used as alternative or for salvage therapy
Trichosporonosis	1st line: Voriconazole	
Scedosporidiosis	Voriconazole + Terbinafine best treatment available	

Antifungal resistance

1-Emerging antifungal-resistant IFIs are the new threat to these heavily immunosuppressed patients.

2-Early specific risk-based antifungal strategies such as prophylaxis, pre-emptive and empirical therapies, are common practices in HM patients.

3-long-term exposure to antifungal agents (voriconazole and echinocandins), the major driving force for the development of resistance.

4-Neutropenia induced by chemotherapy reduces the pharmacodynamic response to antifungal medications and lengthens therapeutic durations.

Antifungal resistance

5-The surfaces of indwelling catheters, particularly central venous catheters, are frequently covered by biofilms that prevent drugs from penetrating deeper, making the fungus resistant to therapy.

6-Suboptimal antifungal drug levels of certain antifungal agents (such as triazoles) due to their nonlinear pharmacokinetics, and fungal infections of sites with poor drug delivery leading to exposure to possibly subtherapeutic drug concentrations, favor the development of resistance.

7-The global upsurge of fungal pathogens intrinsically resistant to antifungal agents, such as Candida auris and Aspergillus terreus with fewer available treatment option, further raise the concern.

Breakthrough fungal infections (BFI)

1-Although the widespread use of antifungal prophylaxis in recent years, has led to an overall reduction of IFIs in patients with HM,

2-subset of such patients still develops BFI which has a substantial impact on attributable mortality

3-The severity and frequency of BFI depend on the local epidemiology, antifungal treatment, and patient characteristics.

4-During remission-induction chemotherapy in newly diagnosed HM, BFIs are less frequent and are mostly IA

5-during prophylaxis for long-standing refractory/relapsed HMs, BFIs are more frequent, commonly with inherently resistant non-Aspergillus fungus

Therapeutic drug monitoring (TDM)

1-the serum concentration of voriconazole has a strong association with plasma drug concentration, and toxicity

2-Voriconazole TDM is highly advised with a target plasma concentration of 1–6 mg/L for prophylaxis, within 2–5 days of treatment beginning

3-Although routine TDM of posaconazole is not recommended, it may offer an advantage in evaluating compliance or absorption in cases of clinical failure or verifying breakthrough IFI

Conclusions: Invasive Fungal Infections

Way to improve IFI are:

- Selective antifungal prophylaxis- risk based
- Aggressive diagnostic approach- nonculture methods
- High degree of vigilance
- Early pre-emptive therapy
- Develop less damaging methods of immune suppression
- Immunomodulation in very high risk patients

Conclusion

1-There is a need for heightened vigilance and increased awareness of IFI in patients with HMs in view of changing fungal epidemiology.

2-The diagnosis of IFIs cannot be based solely on clinical symptoms and requires further microbiological and imaging diagnostic procedures.

3-The diagnosis is categorized into “proven,” “probable,” and “possible” IFI.

4-In the absence of culture-based evidence, the best diagnostic precision can be attained using the combination testing of GM with BDG or PCR.

5-Treatment and prophylaxis strategies are based on the risk categories of the patients. 6-Emerging antifungal-resistant and breakthrough infections are the new challenges in the management of IFIs.

7-TDM of Voriconazole is strongly recommended.

8-Environmental control with HEPA filters and protective isolation is crucial to the prevention of IFI.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